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10/661,217	09/12/2003	Steven Willem Jan Lamberts	50318/004001	7547

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,217	LAMBERTS ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *4-7 and 15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/26/04; 9/2/03*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I, claims 1-3 and 8-14 in the reply filed on April 14, 2006 is acknowledged. Applicant's response did not specifically traverse the election requirement as it pertains to the restriction between groups I-VI.

The response does argue that the format of claims 8-12 is proper and that claims 8-12 (and non-elected claim 15) were not presented in an improper Markush format. It is stated that it acceptable to recite all of the alternative limitations within a single claim.

This argument is not persuasive because, as set forth in MPEP 83.02, " (t)he members of the Markush group (A, B, and C in the example above) ordinarily must belong to a recognized physical or chemical class or to an art-recognized class. However, when the Markush group occurs in a claim reciting a process or a combination (not a single compound), it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is mainly responsible for their function in the claimed relationship, and it is clear from their very nature or from the prior art that all of them possess this property. " The members of the Markush group recited in claims 8-12 do not possess a common property because the Markush group includes members drawn to distinct methods, such that the methods of group I (claim 1) are drawn to methods for detecting the risk of a metabolic disorder, whereas the methods of group II (claim 4) are drawn to methods for predicting longevity and the methods of group III (claim 5) are drawn to methods for determining the dose of a glucocorticoid. Metabolic disorders, longevity and dosages of glucocorticoids are not

of the same nature and do not possess a common feature. Again, it is noted that the response does not present any arguments as to why restriction between these distinct methods would not be considered to be proper.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

2. Claims 8-12 are objected to because the claims include subject matter of and are dependent from the non-elected claims.

3. Claim 14 is objected to because of the following informalities:

In claim 14, "ER22/23KK" should read "ER22/23EK"

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 8-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of screening a human subject age 53 to 82 from the Netherlands for a propensity for lower fasting insulin concentrations

and lower total cholesterol and LDL concentrations wherein the methods comprise obtaining from said subject a nucleic acid sample containing the glucocorticoid receptor (GR) gene, directly assaying the GR gene for the presence of a ER22/23EK polymorphism and determining the likelihood that the individual will have lower fasting insulin levels or lower total or LDL cholesterol concentrations, wherein the presence of the ER22/23EK polymorphism is indicative of increased likelihood of lower fasting insulin levels and lower total and LDL cholesterol concentrations as compared to control subjects lacking the ER22/23EK polymorphism, does not reasonably provide enablement for methods for determining the risk of any individual developing any metabolic disorder by assaying for the ER22/23EK GR polymorphism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1-3 and 8-12 are drawn broadly to encompass methods for determining the likelihood that an individual will develop a metabolic disorder by assaying for the ER22/23EK polymorphism in the glucocorticoid receptor gene. Claim 13 is drawn to methods for determining whether a treatment regimen is suitable for an individual having a metabolic disorder by assaying for the ER22/23EK polymorphism. Claim 14 is drawn to methods for diagnosing and treating an individual susceptible to a metabolic disorder by assaying for the ER22/23EK polymorphism.

The specification at page 5 states that the invention provides a methods for determining the risk of an individual developing a metabolic disorder. The specification then states that the method can be used to assess whether the individual may develop a metabolic disorder in the future. The specification goes on to state that "(t)the metabolic disease is selected from cardiovascular disease, diabetes mellitus, glucose intolerance/insulin resistance, dyslipidemia (hypercholesterolemia in particular) and (metabolic) Syndrome X." Since this passage refers to metabolic diseases rather than the claimed metabolic disorders and since the specification does not specifically state that metabolic disorders are intended to include only the stated conditions, it is unclear as to whether the claims are intended to be limited to only methods which determine risk of cardiovascular disease, diabetes mellitus, glucose intolerance/insulin resistance, dyslipidemia (hypercholesterolemia in particular) and (metabolic) Syndrome X. In the absence of a clear definition for metabolic disorders, the claims have been interpreted as including methods which determine risk for any metabolic disorder wherein the disorder is any one of the disorders recited above, or any of the other significantly

divergent types of metabolic disorder including phenylketonuria, amyloidosis, mucolipidoses, hypokalemia, hypercalcemia, hypocalcemia, Tay-Sachs, Leukodystrophies, lysosomal disorders, and Wilson's disease.

The claims further include methods which screen any individual for risk of a metabolic disorder. The claims include analyzing human subjects of any ethnic background and of any age. The claims also include analyzing non-human subjects.

Additionally, claims 13-14 encompass determining whether a treatment regimen is suitable for an individual with a metabolic disorder. The claims do not specify a particular type of treatment and do not specify how one would ascertain the suitability of the treatment based on the presence of the ER22/23EK polymorphism.

Nature of the Invention

The claims encompass methods of determining the risk of a metabolic disorder by detecting the presence or absence of the ER22/23EK GR polymorphism. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification (page 1) teaches the occurrence of a ER22/23EK polymorphism in the GR gene. This polymorphism consists of a point mutation in codon 22 changing GAG to GAA, leading to a silent mutation in the GR protein and a point mutation in codon 23 which changes an AAG to AAG, leading to an arginine to lysine substitution.

The specification also teaches the results of a study regarding the frequency of the ER22/23EK polymorphism in a sample population of 202 human subjects, ages 53 to 82, living in a suburb of Rotterdam, Netherlands (see page 19). In this study group, 18/202 individuals (8.9%) were heterozygous for the ER22/23EK polymorphism. No individuals were homozygous for the polymorphism. The polymorphism was found to be present at a higher (12.9%) frequency in subjects 67 to 82 years of age as compared to subjects 53 to 67 years of age (see page 22).

Carriers of the ER22/23EK polymorphism showed lower total cholesterol and LDL-cholesterol levels (page 27). They also "tended" to have lower fasting insulin concentrations before and after DEX treatment (page 25).

There was no difference between ER22/23EK carriers and non-carriers for: serum insulin concentrations following DEX administration; fasting glucose concentrations; change in glucose levels in response to DEX administration; IGF-BPI levels, HDL-cholesterol and triglyceride concentrations; or concentrations of estradiol, SHBG, androstenedione, DHEA-S or testosterone. In addition, no association was found between the occurrence of the polymorphism and intermittent claudication, angina pectoris, or myocardial infarction.

Despite the lack of correlation between the polymorphism and the above conditions/responses, the specification broadly concludes that individuals with the ER22/23EK polymorphisms have a "healthier metabolic profile than non-carriers" (page 31). It is stated that there is a lower risk for atherosclerotic plaques in carriers versus non-carriers when the data is adjusted for age. Further, with an additional adjustment

for cholesterol, the significance of the association "disappeared, which indicates that the lower cholesterol levels explain most of the lower risk on the presence of plaques in the carotid artery." Based on these findings, the specification concludes that the ER22/23EK polymorphism can be used to determine the risk of any metabolic disorder and particularly can be used to determine the occurrence or risk of developing cardiovascular disease, diabetes mellitus, glucose intolerance/insulin resistance, dyslipidemia (hypercholesterolemia in particular) and (metabolic) Syndrome X.

The specification does not specifically analyze the occurrence of the polymorphism in individuals having a particular metabolic disease. Further, no data is presented regarding the frequency of the polymorphism and any risk factors or metabolic diseases in individuals of an age less than 53 years old or in individuals having ethnic backgrounds outside of the Netherlands. There is also no disclosure of the occurrence of the ER22/23EK polymorphism in non-human subjects and thereby no disclosure of an association between this polymorphism and any risk factors or metabolic disorders in non-human subjects.

Regarding claims 11 and 12, the claims are inclusive of agents, and particularly antibodies, which distinguish between the wild-type GR protein and the variant GR protein having the R23K polymorphism. However, there is no disclosure in the specification or prior art of an antibody or other agent that is able to specifically bind to and detect the variant protein which differs from the wild-type protein by only one amino acid substitution at amino acid position 23.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of determining an association between a condition and a polymorphism is highly unpredictable. Knowledge of the occurrence of a polymorphism does not allow one to immediately envision which specific disorders or phenotypes will be correlated with the occurrence of the polymorphism.

The results set forth in the specification are limited to specific responses and phenotypes that represent a risk factor, amongst many other risk factors, for susceptibility to particular metabolic disorders. There is no information is provided in the specification or in the prior art regarding the frequency of the ER22/23EK polymorphism in individual's having specific metabolic disorders, such as diabetes mellitus, glucose intolerance or any particular cardiovascular disorder. In fact, subjects with endocrine disorders, including subjects being treated for diabetes mellitus were excluded from the study discussed in the specification. The teachings in the specification do not clarify why the lack of an association between the polymorphism and the majority of the risk factors examined, including triglyceride levels and HDL levels, may be ignored while the associations between total cholesterol, LDL cholesterol and fasting insulin levels alone would be sufficient to establish a propensity for any metabolic disorder. Triglyceride and HDL levels, for instance, are known to be important factors in determining the risk for cardiovascular disease. A lack of an association between triglyceride and HDL levels and the polymorphism would seem to indicate that the polymorphism alone cannot be used to determine an individual's propensity for having or developing a cardiovascular disorder or other metabolic disorder. In such complex diseases as cardiovascular disorders and diabetes, many factors influence susceptibility to a disease. In fact, the

specification itself teaches that the cardiovascular-related diseases of intermittent claudication, angina pectoris, and myocardial infarction were not associated with the ER22/23EK polymorphism. Thereby, a showing of an association between the polymorphism and a particular response or phenotype is not sufficient to allow one to conclude that the presence or absence of the ER22/23EK polymorphism is a risk factor for any and all metabolic disorders.

Also, the specification (page 22) teaches that the ER22/23EK polymorphism was found in 8.9% of the study group. If the ER22/23EK polymorphism is in fact associated with low risk of all metabolic disorders, and absence of the polymorphism is associated with high risk of all metabolic disorders, then one would be lead to the conclusion that 91.1% of the general population is at risk of developing, for example, cardiovascular disease or diabetes mellitus. Such a conclusion would not be consistent with the frequency of these and other metabolic disorders in the general population.

Further, the specification does not teach a particular structure/function relationship between the polymorphism and disease as would be necessary to extrapolate the findings obtained between the polymorphism and cholesterol levels to all types of metabolic disorders. The specification (page 1-2) states that "(t)hese mutations have been shown not to alter the activity of GR in 'in vitro' experiments." The specification does not disclose any mechanistic effect of the polymorphism on the glucocorticoid receptor. Only by performing additional trial-by-error experimentation can one determine which, if any, specific metabolic disorders are associated with the presence of the GR polymorphism.

The teachings of Lucentini (The Scientist. December 2004, page 20) highlights the unpredictability in the art of establishing an association between a polymorphism and the occurrence of a disease or condition. As discussed by Lucentini, reproducible association studies are "few and far between." The reference reports that "when a finding is first published linking a given gene with a complex disease, there is only roughly a one third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated. The first finding is usually 'spurious, or it is true, but it happens to be really exaggerated, ' ...there may be no way to predict which new gene-association studies will be verified with multiple replication."

Additionally, it is highly unpredictable as to whether the results obtained in the present study group can be extrapolated to the general population. The teachings in the specification are limited to the frequency of the ER22/23EK polymorphism in a very specific group – individuals from a suburb of the Netherlands ages 53 to 82. No information is provided regarding the frequency of the mutation in diverse ethnic populations or in individuals less than 53 years old. Given the well known variation in the frequency of alleles in different ethnic populations and the significance of age on conditions associated with diabetes, cardiovascular disorders etc, the findings set forth in the specification regarding this one particular population cannot be extrapolated to a representative number of other ethnic populations and age groups.

The post-filing date art supports the unpredictability of extrapolating the results obtained in the present study to other populations. For instance, van Rossum (The Journal of Clinical Endocrinology and Metabolism. 2004. 89:4004-4009) teaches that in

young adults, the ER22/23EK is associated with body composition in a sex-specific manner. Yet, the present specification does not teach that there is a gender-specific association between the polymorphism and particular risk factors in young-adults. The reference (page 4008) also notes that as of 2004, the mechanism of the ER22/23EK polymorphism at the molecular level remained unknown.

Amount of Direction or Guidance Provided by the Specification:

The specification has not provided sufficient guidance as to how to extrapolate the findings obtained with total and LDL cholesterol and lower fasting insulin levels to all types of metabolic disorders. The specification does not teach how to interpret the limited information provided therein and does not teach how to use this information to determine an association between the ER22/23EK polymorphism and any metabolic disorder. There is insufficient guidance provided as to how to interpret and apply the results in the specification which clearly teach that the polymorphism is NOT associated with the metabolic risk factors of serum insulin concentrations following DEX administration; fasting glucose concentrations; change in glucose in response to DEX administration; IGF-BPI levels, HDL-cholesterol and triglyceride concentrations; concentrations of estradiol, SHBG, androstenedione, DHEA-S or testosterone; intermittent claudication, angina pectoris, or myocardial infarction.

While methods for identifying polymorphisms and determining their frequency in study populations are known in the art, such methods provide only the general guidelines that allow researchers to randomly try to establish an association between a polymorphism and a disorder. In complex disorders such as metabolic diseases,

knowledge of an association between a polymorphism and certain risk factors is not sufficient to establish a clear correlation between the polymorphism and the disease itself, particularly when the polymorphism has been shown to lack a correlation with other known risk factors. Accordingly, providing general methods for screening populations for a polymorphism in an attempt to determine whether the polymorphism is linked to a disease does not constitute sufficient guidance. Such teachings provide only an invitation to experiment.

Moreover, the claims as broadly written include the detection of ER22/23EK polymorphism in any "individual." Since the term "individual" has not been defined in the specification, this term has been interpreted as including non-human subjects. However, the specification does not disclose the existence of the polymorphism in any particular non-human subjects. Further, the specification has not provided any specific guidance as to how to how to use the ER22/23EK polymorphism to determine the risk of metabolic disorders in non-human subjects. No specific guidance is provided in the specification as to how to predictably extrapolate the findings obtained in humans to other organisms.

Regarding claims 11 and 12, the specification and prior art do not provide sufficient guidance to enable the generation and use of antibodies or other agents which are able to bind specifically to the mutant GR protein having the R23K mutation and which can thereby distinguish between the wild-type and mutant alleles. The specification (e.g., page 15) teaches broadly that an antibody may be used to specifically detect the ER22/23EK polymorphism, but does not exemplify such a

polymorphism. It is unpredictable as to whether the change of one amino acid from an arginine to a lysine would be sufficient to result in the production of antibodies that can differentiate between the 2 alleles of the GR protein. In some cases, an antibody elected by one antigen can cross-react with a different antigen if the two different antigens share an identical or very similar epitope (Glodsby et al. 2003, page 141). With regard to the presently claimed amino acid change, it is not known whether this amino acid change occurs in an antibody binding epitope. In the absence of knowledge regarding the binding epitopes and the effects of the polymorphism on these epitopes, it is difficult to predict whether or not any generated antibodies would be able to function to differentiate the two alleles. Since the present claims require the use of an antibody or agent that differentiates between the 2 alleles, it remains unpredictable as to whether such methods can be performed because sufficient guidance has not been provided to allow for the generation of an antibody or other agent to perform such an assay.

Regarding claims 13 and 14, the specification has not provided sufficient guidance as to how to determine whether a treatment regimen is suitable for an individual having a metabolic disorder. There is no specific disclosure in the specification of an association between the ER22/23EK polymorphism and a particular type of treatment or response to treatment. The teachings in the specification indicate that individuals 53 to 82 with the ER22/23EK polymorphism have a lower risk of having high total cholesterol levels. The specification does not teach any particular therapy that would be used to treat individuals with low total cholesterol levels. There is no guidance provided in the specification as to how to select a therapy to administer to carriers of the

polymorphism an "effective amount of an agent which prevents or treats a metabolic disorder" particularly since such individuals would not appear to be in need of treatment if they are at low risk of developing a metabolic disorder. There is also no specific guidance provided as to the criteria to be used to select a treatment regimen that is "suitable for an individual having a metabolic disorder" wherein "the suitability of treatment depends on the presence or absence of the ER22/23EK polymorphism." A clear correlation between any treatment regimens and the ER22/23EK polymorphism has not been established.

Working Examples:

Again, the specification teaches methods for analyzing the nucleic acids of a human directly to detect the presence of the ER22/23EK polymorphism in the GR gene. The specification exemplifies the use of this methodology to establish that individuals from the Netherlands ages 53 to 82 who carry the ER22/23EK polymorphism have a lower total and LDL cholesterol level and a lower fasting insulin level.

However, no working examples are provided in which the ER22/23EK polymorphism is used to ascertain the risk of a subject having or developing a particular metabolic disorder. Further, no working examples are provided in which individuals outside of the study group of individuals from the Netherlands ages 53 to 82 are analyzed for the ER22/23EK polymorphism in order to determine the likelihood that such individuals will have risk factors for metabolic disorders or will have or will develop metabolic disorders.

There are also no working examples in which non-human subjects are diagnosed for a metabolic disorder by assaying for the ER22/23K polymorphism.

There are no working examples in which a treatment regimen for subjects having a metabolic disorder is determined based on the presence of the ER22/23K polymorphism.

There are no working examples in which the ER22/23K polymorphism is detected using an antibody or other protein binding agent that specifically distinguishes between the 23arg and 23lys alleles of the GR protein.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification teaches only an association between the risk factors of total cholesterol levels and fasting insulin concentrations and the ER22/23EK polymorphism. The specification does not teach that the association of the polymorphism with these risk factors alone are sufficient to establish a more general association between the polymorphism and the broadly claimed genus of metabolic disorders, including diabetes mellitus and any type of cardiovascular disease. Further, the scope of the claims is not commensurate with the teachings in the specification because the results provided in the specification are limited to a very specific study group, i.e., individuals 53-82 from the Netherlands. However, the claims are inclusive of methods which analyze any ethnic group and any age group for their susceptibility to a metabolic disorder. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite over the recitation of "suitable for an individual having a metabolic disorder." The claim does not set forth the criteria for determining whether a treatment is suitable nor the criteria for determining whether a treatment is suitable based on the presence or absence of the ER22/23EK polymorphism. Accordingly, one cannot determine the meets and bounds of the claimed subject matter.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by van Rossum (Diabetes. Oct. 2002; cited in the IDS).

It is noted that the inventorship of the present application is distinct from the authorship of the van Rossum et al reference and that the van Rossum reference was published prior to the filing of the priority document 0224559.5.

van Rossum teaches methods comprising detecting in a sample from an individual the presence or absence of the ER22/23EK polymorphism in the GR gene (see page 3129). The authors interpreted the results of the determination step as indicating that the individuals carrying the ER22/23EK polymorphism have a better metabolic health profile as compared to noncarriers (see page 3133). van Rossum studied the association between the ER22/23EK polymorphism and risk factors associated with cardiovascular disease and insulin levels/intolerance. Thereby, the

methods of van Rossum include a step of determining the likelihood that an individual will develop a metabolic disorder wherein the presence of the ER22/23EK polymorphism is indicative of a low risk of developing a metabolic disorder and the absence of the ER22/23EK polymorphism is indicative of a high risk of developing a metabolic disorder. It is noted that the results set forth in the van Rossum reference are identical to those set forth in the present application and that the interpretation of those results, i.e., an association between the ER22/23EK polymorphism and risk factors for coronary heart disease and diabetes, are also equivalent to those required by the present claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Rossum in view of Cotton (Advances in Genome Biology. 1991. 1: 253-300)

The teachings of van Rossum are presented above. Regarding claims 8-10, van Rossum teaches detecting the polymorphism by RFLP analysis. The reference does not teach using a probe to detect the polymorphism.

However, Cotton teaches methods for detecting point mutations in nucleic acid sequences. In particular, Cotton (page 277) teaches that allele-specific probes can be used in hybridization assays to detect the presence of a single nucleotide change.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of van Rossum so as to have performed a hybridization reaction with an allele-specific probe in place of RFLP analysis in order to have provided an equally effective and rapid means for detecting the ER22/23EK polymorphism.

9. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Rossum.

The teachings of van Rossum are presented above. Van Rossum does not teach determining a suitable therapy based on the presence or absence of the polymorphism. However, van Rossum teaches that the individuals with the ER22/23EK polymorphism have a healthy metabolic profile and individuals lacking the ER22/23EK polymorphism thereby have a poor metabolic profile. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made administered a convention treatment for improving, for instance, cholesterol levels in subjects lacking the

ER22/23EK polymorphism in order to lower the risk of those subjects developing a metabolic disorder associated with high cholesterol levels.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
May 8, 2006

CARLA J. MYERS
PRIMARY EXAMINER